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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/410,336	LOVE ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2002 and 28 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on November 6, 2002 in Paper No. 23 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/410,336 is acceptable and a CPA has been established. An action on the CPA follows.

2. The notice of appeal filed July 11, 2002 in Paper No. 21 is acknowledged and has been entered.

3. The amendment filed June 11, 2002 in Paper No. 18 has been entered. Claims 17-32 have been canceled. Claims 1, 5, 9, and 13 have been amended.

4. Claims 1-16 are pending in the application and are currently under continued prosecution.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed March 11, 2002 (Paper No. 17) have been withdrawn.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reason set forth in section 14 of the Office action mailed March 11, 2002 (Paper No. 17).

Claim 5 recites the term "cancer cell specific identifying agent"; however, as noted in the Office action mailed March 11, 2002, there does not appear to be proper and sufficient antecedent basis in the specification to support the recitation of this term in the claims.

Applicants have traversed this ground of rejection in Paper No. 25 arguing that the originally filed specification clearly indicates that Applicants had possession of the claimed invention at that time application was filed. In support of this assertion, Applicants have referred to the disclosure set forth on pages 10 and 11, which Applicants state expressly discloses the use of different types of identifying agents that will bind specifically to cancerous or pre-cancerous cells. In addition, Applicants have referred to the disclosure on page 14 and 15, which Applicants state expressly discloses cancer specific targeting agents.

Applicants' arguments have been carefully considered but not found persuasive. The disclosures on pages 10, 11, 14, and 15 to which Applicants have referred do not appear to provide proper and sufficient antecedent basis for the recitation of the term "cancer cell specific identifying agent". For example, at page 10, the specification discloses, "the identifying agent will be specific for a cell membrane bound target" (lines 27 and 28), but this disclosure does not provide proper and sufficient support for a recitation of a requirement that the identifying agent be specific for cancer cells. Furthermore, the examples of identifying agents set forth in the disclosures on pages 14 and 15 do not provide support for the breadth of the term; and, it is noted that many of the disclosed antibodies, which bind antigens such as ErbB-2, are not cancer cell specific, since normal, non-cancerous cells also express the antigens to which these antibodies bind.

Again, this issue might be resolved if Applicants were to either point to specific disclosures in the specification that are believed to provide the necessary support, or

amend the claims to recite a limitation using the explicit language set forth in the specification.

8. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 5 presently recite, "identifying the location of premalignant or malignant cells within a breast duct or breast ductal network", whereas previously the claims recited a limitation requiring the pre-malignant or malignant cells to be breast cancer cells. There does not appear to be proper and sufficient antecedent basis in the specification to support the recitation of the phrase in the present claims. The specification discloses, "[t]he present invention relates generally to medical methods for identifying, diagnosing and treating **breast** cancer" (emphasis added; page 1, lines 9 and 10). There does not appear to be any disclosure that invention can be used to identify other types of pre-malignant or malignant cells so as to support the breadth of the present claims. The recitation of the phrase in the present claims therefore appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph.

This issue might be resolved if Applicants were to point to specific disclosures that are believed to provide the necessary support for the broader scope of the present claims.

9. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 5, 9, and 13 recite, "allowing [...] unbound portions of the delivered [compound or identifying agent] to be eliminated from said at least one duct". Additionally, claims 9 and 13 recite, "determining the lymph node involvement after said

unbound portions of the delivered [compound or identifying agent] have exited said at least one breast duct". However, there does not appear to be proper and sufficient antecedent basis in the specification to support the recitation of these limitations in the claims. Applicants have not stated wherein the specification support for the recitation of these limitations is found. The Examiner notes, while the specification discloses, "the assessed breasts were washed with saline solution to remove nonspecifically bound immunoliposomes" (page 16, lines 30 and 31; and page 17, lines 28 and 29), these disclosures do not appear to provide the necessary explicit, expressive, or implicit support. Therefore, the recitations of these limitations in the present claims appear to introduce new matter and thereby violate the written description requirement set forth under 35 USC § 112, first paragraph.

These issues might be resolved if Applicants were to point to specific disclosures that are believed to provide adequate support for the recitation of these limitations in the present claims.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 10 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 14 are indefinite because claims 10 and 14 recite, "wherein detecting [...]". However, there is no antecedent basis in the claim 9 and 13 from which claims 10 and 14 depend.

12. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete because claims 1, 5, 9 and 13 omit one or more essential steps, such omission amounting to a gap between the steps for the reason stated in the preceding Office Action mailed March 11, 2002 (Paper No. 17).

Applicants have traversed these grounds of rejection reiterating the arguments set forth in reply to previous Office actions. Applicants' arguments have again been carefully considered but not found persuasive.

In traversing this rejection, Applicants have noted that MPEP § 2172.01 states that essential matter is defined as elements, steps or the like that are described by the Applicants in the specification as essential to practicing the invention. The same section of the MPEP was cited in the previous Office action to support the maintenance of these grounds of rejection. As noted in the previous Office action mailed March 11, 2002, because the specification teaches that the omitted steps are essential to the practice of the invention, the omission of these essential steps in the claims are proper grounds for the rejection of those claims under 35 USC § 112, second paragraph.

Additionally, Applicants have argued that it is not necessary to provide factual evidence that the steps are not essential, as the teachings of the specification suggest; rather Applicants have argued that the burden is upon the Office to show that essential steps have been omitted. In reply to this argument, the specification teaches that the omitted steps are essential, since all examples set forth therein teach the necessity of detecting the identifying agent or targeting agent coupled to an identifying agent by MRI and correlating the data so acquired with information gained by repeated physical examination and/or mammogram to assign a location to the pre-malignant or malignant cells within the breast duct, breast ductal network, or lymph nodes; and the burden of establishing the *prima facie* case was thus met in the first Office action.

13. Claims 9-16 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which Applicants regard as their invention. Evidence that claims 9-16 fail to correspond in scope with that which Applicants regard as the invention was identified in the Office action mailed March 11, 2002 (Paper No. 17).

Applicants have traversed this ground of rejection in Paper No. 25 arguing that the issue was fully and completely addressed in the amendment filed June 11, 2002 (Paper No. 18). In particular, Applicants have remarked that the arguments are set forth

on pages 3-6, and especially those on pages 5 and 6 of the amendment traverse this ground of rejection.

Applicants' remarks have been carefully considered, however the arguments set forth on pages 3-6 of the amendment filed June 11, 2002 do not appear to address this ground of rejection.

As stated in the Office action mailed March 11, 2002, the claims are drawn to a method for determining whether the lymph nodes are involved in patients diagnosed with pre-malignant or malignant breast cancer growths. As further stated, contrary to Applicants' remarks, the present invention does not relate to *in vivo* determinations of the presence of cancerous or pre-cancerous cells by identifying *only* the location of a cancerous or pre-cancerous cell in the breast duct or breast ductal network. Instead, since the claims recite that the patients have been diagnosed with pre-malignant or malignant breast cancer growths, the location of the cancerous or pre-cancerous cells in the breast duct or breast ductal network must be already known and according to the claims, the objective of the method is to determine if the lymph nodes have become involved in the disease. Accordingly, Applicants' remarks in the amendment filed June 11, 2002 suggest that claims 9-16 fail to correspond in scope with that which Applicants regard as the invention. Although Applicants have asserted that this ground of rejection has been fully and completely addressed, Applicants have not clarified the record by resolving the discrepancy, since identifying *only* the location of a cancerous or pre-cancerous cell in the breast duct or breast ductal network could not lead to a determination of lymph node involvement.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 5-8 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hou, et al (*Radiology* **195**: 568-569, 1995), as evidenced by Van Zee, et al (*Cancer* **82**: 1874-1880, 1998) and Canto, et al (*Gastrointestinal Endoscopy* **44**: 1-7, 1996).

The following is essentially a reiteration of the grounds of rejection set forth in the Office action mailed March 11, 2002 (Paper No. 17).

Hou, et al teach a comprising providing a pre-malignant or malignant cancer cell specific identifying agent, namely methylene blue, which as evidenced by the teachings of Canto, et al is capable of binding selectively to pre-malignant, or dysplastic cells, and to malignant cells.

Although Canto, et al does not explicity teach methylene blue is a pre-malignant or malignant cancer cell specific identifying agent, as noted in the Office action mailed March 11, 2002 (Paper No. 17), the specification does not define the term "cancer specific identifying agent". Accordingly, as also noted in the previous Office action mailed March 11, 2002, the American Heritage® Dictionary of the English Language: Fourth Edition, 2000, defines "specific" as "[r]elating to, characterizing, or distinguishing a species" (Copyright © 2000 by Houghton Mifflin Company). Thus, a "cancer specific identifying agent" in the context of the claim would be reasonably defined as an identifying agent that distinguishes breast cancer tissue from normal breast tissue. Because methylene blue selectively stains pre-malignant or malignant tissue differentially relative to normal tissue and enables the clinician to distinguish pre-cancerous and cancerous tissue from normal tissue, it would appear that methylene blue is a "cancer specific identifying agent". This conclusion is further supported by the disclosure by Hou, et al stating, "the duct and any involved lobules could be identified by the presence of the blue dye" (page 568, column 3).

Hou, et al teach delivering the identifying agent through at least one breast duct by cannulation or catheterization of the one or more breast ducts.

Hou, et al teach allowing the delivered identifying agent to bind pre-malignant or malignant cells within the breast duct or breast ductal network. Although Hou, et al do not explicitly teach allowing unbound portions of the delivered identifying agent to be

eliminated from the breast duct, the elimination of the unbound portions of the identifying agent will occur naturally as a result of the process.

Hou, et al teach identifying the location of the pre-malignant or malignant cell bound to the identifying agent within the breast duct or breast ductal network. Hou, et al teach that the identifying agent was injected into the patient through a breast duct in a sufficient amount to facilitate localization of a breast lesion before surgical excision was performed to remove the pre-malignant or malignant cancerous cells from the patient (page 568, column 3). As evidenced by Van Zee, et al the process of Hou, et al is intended to enable the practitioner to localize pre-malignant or malignant tissue in the breast.

All of the limitations of the claims are thus met by the teachings of Hou, et al.

Applicants have traversed this ground of rejection arguing that Hou, et al does not anticipate the claimed invention because Hou, et al teaches the use of methylene blue, which Applicants assert is not specific to cancer cells. Additionally, Applicants have argued that Hou, et al does not anticipate the claimed invention because Hou, et al does not explicitly teach the step of *allowing* the identifying agent to bind pre-malignant or malignant cells within the breast duct or ductal network and *allowing* unbound portions of the delivered identifying agent to be eliminated.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons.

Although Applicants have asserted that methylene blue "does not bind only to cancer cells", the term "cancer specific identifying agent" is not defined in the specification, so the term is not limited to an identifying agent that binds *exclusively* to cancer cells. For the reasons set forth in the previous Office action mailed March 11, 2002 (Paper No. 17) and reiterated above, methylene blue is deemed the same as the identifying agent to which the claims refer.

Additionally, the specification provides examples of monoclonal antibodies that are presumed to be suitable "cancer specific identifying agents". As noted in the Office action mailed March 11, 2002, one of these identifying agents is a monoclonal antibody

that binds ErbB-2, which can be used to identify cancer cells; but cancer cells alone do not express ErbB-2, since normal cells also express the antigen. Therefore, the present claims do not read on a method comprising delivering an identifying agent that binds exclusively to cancer cells, as Applicants have asserted, but rather on the prior art.

In reply to Applicants' argument that Hou, et al does not teach the step of *allowing* the identifying agent to bind pre-malignant or malignant cells within the breast duct, to the contrary, Hou, et al discloses that pre-malignant or malignant cells within the breast duct were identified by virtue of the binding of the identifying agent, namely methylene blue to the cells. Therefore, the method of Hou, et al necessarily *allows* the identifying agent to bind the cells. This conclusion is evidenced by the teachings of Canto, et al (*Gastrointestinal Endoscopy* **44**: 1-7, 1996). Canto, et al teach methylene blue selectively stains pre-cancerous and cancerous cells; therefore, methylene blue will bind pre-cancerous and cancerous cells.

In reply to Applicants' argument that Hou, et al does not teach the step of *allowing* the unbound portions of the delivered identifying agent to be eliminated, it appears that this is a passive step - allowing unbound portions to be eliminated appears to require no active step or participation by the practitioner. Practicing the method of Hou, et al will inherently lead to allowing unbound identifying agent to be eliminated by natural processes. Therefore, the method of Hou, et al is deemed the same as the method of the claims, absent a showing of any difference.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hou, et al (*Radiology* **195**: 568-569, 1995) in view of Allan, et *al (British Journal of*

Cancer **67**: 706-712, 1993) and Vitetta, et al (*Cancer Research* **54**: 5301-5309, 1994), as evidenced by Krag, et al (*New England Journal of Medicine* **339**: 941-946, 1998).

The following ground of rejection is essentially a reiteration of the ground of rejection set forth in the first Office action mailed March 9, 2001 (Paper No. 9). However, modifications have been made to address the new limitations of the present claims.

Hou, et al teach what was set forth in the 35 USC § 102(b) rejection above, but do not expressly disclose that the method can be used to determine whether or not there is lymph node involvement in patients diagnosed with pre-malignant or malignant cancer growths, wherein said method comprises a step of detecting the identifying agent in a sentinel lymph node. Also, Hou, et al do not teach that an identifying agent that is coupled to a targeting molecule can be used in place of the identifying agent, not coupled to a targeting molecule, when practicing the diagnostic method. Furthermore, Hou, et al does not expressly disclose allowing any unbound identifying agent or coupled compound to be eliminated by natural absorption and clearance in the body so that its removal by the practitioner is not required.

Allan, et al teach a method for the radioimmunolocalization of breast cancer to facilitate surgical excision of the tissue surrounding and including the malignant breast cancer cells and for the determination of lymph node involvement in patients diagnosed with breast cancer (abstract). Allan, et al teach that a patient diagnosed with breast cancer can be injected intravenously with an identifying agent that is coupled to a targeting molecule (page 708, column 1). Specifically, all patients used in the study had primary breast cancer and were recruited prior to surgical management of the axilla (page 706, column 2). The patients were injected with radiolabeled ICR12 in a sufficient amount to enable the clinician to identify the location of malignant cells in the breast and lymph nodes upon imaging using a gamma camera (page 708, column 1 and page 710, Table I). The targeting molecule is ICR12, an antibody capable of specific binding to a tumor cell marker expressed by the proto-oncogene *c-erbB-2* and which is over-expressed in breast cancer (page 706, column 1-2). ICR12 is coupled to an identifying agent, Technetium-99m, a radioisotope that is easily detected by a gamma imaging

camera (page 707, column 1-2). Allan, et al teach that "our results from the preclinical evaluation experiments and the subsequent clinical evaluation provide support for the hypothesis that the use of a highly specific antibody against a preselected target will improve the prospects for accurate localization of tumour deposits by radioimmunolocalization" (page 710, column 2). Allan, et al conclude, "two patients had strong membrane staining and provided excellent tumor localisation to both breast primary and regional node metastases" (abstract). As evidenced by Krag, et al, an example of a regional lymph node is a sentinel lymph node (abstract). Also, Krag, et al teach that if regional node metastases have been detected in a patient, the sentinel lymph node would be involved, because the sentinel lymph node is "the first stop along the route of lymphatic drainage from a primary tumor" (page 941, column 2). Therefore, Allan, et al teach that the practice of the disclosed method led to the successful detection and localization of malignant breast cancer cells in a sentinel lymph node in a patient diagnosed with breast cancer. The method of Allan, et al does not require that the practitioner remove the unbound coupled compound comprising the radiolabeled antibody from the patient's body. Therefore, allowing the unbound coupled compound to be absorbed and cleared naturally by the body of the patient is implicit in the method of Allan, et al.

Vitetta, et al teach that there are limitations in the use of monoclonal antibodies in cancer therapy but, in particular, monoclonal antibodies that are administered to a patient intravenously may not be able to gain access to a tumor (page 5305, column 1). Another potential drawback is that when a patient is administered heterologous antibodies, an immune response to the antibodies may preclude the efficacy of further courses of therapy (page 5305, column 2). Although, the teachings of Vitetta, et al are specifically drawn to methods of therapy, the issues presented here are equally relevant to methods of diagnosis and breast cancer staging, wherein monoclonal antibodies are used to target identifying agents to particular cells and tissues.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the identifying agent of Allan, et al for the identifying agent of Hou, et al in the method of Hou, et al to deliver the agent to a

patient, because the identifying agent of Allan, et al is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells and because the method of Hou, et al enables one to deliver the agent directly to the targeted site at which the cells are expected to occur in a patient without undue risk of retention of the identifying agent in tissues where the cells are not expected to be found. One would have been motivated to substitute the targeted identifying agent of Allen, et al for the identifying agent of Hou, et al because the increased specificity of the method would enable the clinician to make more accurate identification of the location of malignant breast cancer cells within the duct of a patient's breast and a more accurate determination of lymph node involvement in the patient, taking into account the teachings of Vitetta, et al and Krag, et al. Since the breast ductal network and axilla are the targeted tissues, the use of the targeting agent of Allen, et al in the method of Hou, et al would provide an enormous advantage to the clinician because cannulation of a breast duct would permit direct access to the targeted tissues, enabling a better image to be acquired without using excessive amounts of the identifying agent, and thereby enable a better and more accurate diagnosis without risking harm to the patient by delivering unnecessarily large quantities of antibodies and radioisotopes that may have adverse effects.

Applicants have traversed this ground of rejection reiterating the arguments set forth in reply to the preceding Office action mailed March 11, 2002. In particular, Applicants have argued that no motivation would have existed to combine the teachings of the cited references, impermissible hindsight had to have been used in determining the obviousness of the invention, and no reasonable expectation of successfully practicing the invention would have been had by one of ordinary skill in the art at the time the invention was made. Additionally, Applicants have asserted, "modifying the method of Hou to include an agent that is intended to be eliminated from a duct would destroy the method of Hou" and that picking and choosing parts of a reference while ignoring others is improper.

Applicants' reiterated arguments have again been carefully considered but not found persuasive for the following reasons.

Many of Applicants' remarks have been previously considered and not found persuasive, and therefore Applicants are referred to the preceding Office action for a discussion of the reasons.

In addition, in reply to Applicants' argument that the method of Hou, et al could not be practiced successfully using the antibody of Allan, et al, neither of the references provides a disclosure that would teach away from the claimed invention. As stated in the preceding Office action, there does not appear to be a reason one of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of Hou, et al and Allan, et al to successfully derive the claimed invention. More specifically, there does not appear to be a reason one of ordinary skill in the art would not have had a reasonable expectation of success in modifying the method of Hou, et al to replace the identifying agent of Hou, et al with the identifying agent of Allan, et al. The methods of Hou, et al and Allan, et al had demonstrated success and because the identifying agent of Allan, et al is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells and because the method of Hou, et al enables one to deliver the agent directly to the targeted site at which the cells are expected to occur in a patient, the delivery of the agent of Allan, et al to a patient by the method of Hou, et al would be expected to successfully enable the practitioner to localize pre-malignant or malignant tissue within the patient's breast ductal network or lymph nodes - and without the undue risk of retention of the radioactively labeled identifying agent in tissues where the cells are not expected to be found.

18. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,168,779 A (Barsky, et al; '779) in view of Allan, et *al (British Journal of Cancer* **67**: 706-712, 1993) and Lasfargues, et al (*Journal of the National Cancer Institute* **61**: 967-978, 1978), as evidenced by Krag, et al (*New England Journal of Medicine* **339**: 941-946, 1998).

US 6,168,779 A ('779) teaches methods for accessing breast ducts by a procedure involving catheterization to facilitate the delivery of identifying agents that can be used to identify and thereby locate premalignant or malignant cancerous cells within or near a duct or orifice on a breast of a patient diagnosed with breast cancer. '779 specifically teaches that duct cannulation can be performed in which a catheter is inserted into the lumen of one or more pre-selected ducts on the breast of a patient (column 6, lines 37-42 and also claims 10, 18, and 27). Desired diagnostic material may then be instilled into the duct through the catheter inserted through the breast duct (column 6, lines 54-55). According to '779, a targeting molecule, such as an antibody capable of specifically targeting epithelial cells that display a particular marker on their surface and which is coupled to an identifying agent, such as a dye label, is an example of a diagnostic material that can be delivered to the patient through the breast duct (column 3, lines 4-17). A schematic of the method is provided in Figure 3, which illustrates that an orifice region of a ductal network can be identified and located "with a plurality of markers M lining the epithelium of the duct and extending to the perimeter of the orifice" and "labeled antibodies A can be used to locate and label those markers M which are near the orifice O" (column 4, lines 63-67). '779 teaches "exemplary tissue markers include those present on the ductal epithelium" (abstract). '779 teaches, "an orifice to one or more ductal networks is labeled using a specific binding substance, typically an antibody, specific for a tissue marker present on the orifice" (abstract). Thus, '779 provides a genus of identifying agents that when coupled to a targeting agent that specifically recognizes and binds to a particular cellular marker can be delivered through one or more pre-selected breast ducts in an amount sufficient to identify and locate a species of epithelial cells that display that marker at the cell surface.

'779 teaches what was set forth above, but does not expressly disclose that the diagnostic method can be used to identify the location of pre-malignant or malignant cancerous cells, per se. However, '779 teaches that the diagnostic method can be used to identify a genus of epithelial cells, which includes pre-malignant and malignant ductal epithelial cells, that display a particular tissue marker or cellular antigen to which a

targeting molecule coupled to an detectable, identifying agent, e.g., a radiolabeled antibody, will bind specifically to enable a clinician to identify the location of those cells. It is also noted that '779 does not expressly disclose that the identification of the cells can be for the purpose of excising tissue surrounding and including the cells. Furthermore, '779 does not disclose that the method can be used to determine whether there is lymph node involvement in patients diagnosed with pre-malignant or malignant cancer growths, wherein said method comprises a step of detecting the identifying agent in a sentinel lymph node, nor does '779 expressly disclose allowing any unbound identifying agent or coupled compound to be eliminated by natural absorption and clearance in the body so that its removal by the practitioner is not required.

Allan, et al teach what was set forth in the 35 USC § 103(a) rejection above. As evidenced, by Krag, et al, a sentinel lymph node is a regional lymph node; therefore, the method of Allan, et al can be used to determine lymph node involvement in a patient diagnosed with breast cancer, wherein an identifying agent is detectable in a sentinel lymph node. It is well known in the art that ductal breast cancer is of breast epithelial cell origin, as evidenced by the teachings of Lasfargues, et al. Allen, et al teaches that the gene product of the proto-oncogene, *c-erbB-2* is over-expressed in breast cancer and is therefore an example of a breast epithelial tissue marker. Notably, the method of Allan, et al does not require the practitioner to remove the unbound coupled compound comprising the radiolabeled antibody from the patient's body. Therefore, allowing the unbound coupled compound to be absorbed and cleared naturally by the body of the patient is implicit in the method of Allan, et al.

Lasfargues, et al teach ductal breast cancer is of breast epithelial cell origin.

Based on the teachings of Allen, et al and Lasfargues, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that an anti-ErbB2 antibody coupled to an identifying agent that specifically targets cancerous epithelial cells that over-express ErbB-2 within the breast duct can be used in the method of '779 to identify the location of malignant breast cancer within a breast duct or breast ductal network. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the identifying agent

of Allan, et al in the method of '779, because the identifying agent of Allan, et al is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells that over-express the marker to which the targeting molecule binds. One would have been motivated to substitute the identifying agent of Allan, et al in the method of '779 because the increased specificity of the method would enable the clinician to make more accurate identification of the location of malignant breast cancer cells within the duct of a patient's breast and a more accurate determination of lymph node involvement in the patient.

Applicants have traversed this ground of rejection reiterating the arguments set forth in reply to the preceding Office actions. In particular, Applicants have argued that no motivation would have existed to combine the teachings of the cited references. In addition, Applicants have argued that no reasonable expectation of successfully practicing the invention would have been had by one of ordinary skill in the art at the time the invention was made.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons.

To the extent that Applicants' arguments are reiterated, Applicants' arguments have again been considered and not found persuasive, and Applicants are referred to the reply to Applicant's remarks made in the previous Office action mailed March 11, 2002 (Paper No. 17) for the reasons.

In reply to Applicants' objection to the statement made in the previous Office action that it does not take much imagination to visualize the method of present claims, as also stated in the Office action mailed March 11, 2002, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). As further stated, one would have been motivated to substitute the

identifying agent of Allan, et al in the method of US 6,168,779 A because the increased specificity of the method would enable the clinician to make more accurate identification of the location of malignant breast cancer cells within the duct of a patient's breast and a more accurate determination of lymph node involvement in the patient. Furthermore, Applicants are again reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

As to whether one of ordinary skill in the art would have had a reasonable expectation of successfully deriving the claimed invention given the teachings of the prior art cited as a basis for this rejection, it is not immediately apparent why the modification of the method of Barsky in view of Allan, et al, as proposed in the rejection, would not have successfully arrived at the invention. Contrary to Applicants' opinion, then, there does not appear to be a reason one of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of Barsky and Allan, et al and more specifically modifying the invention of Barsky to in view of Allan, et al to use the identifying agent coupled to the targeting agent of Allan, et al and thereby deriving an invention such as that which is claimed in the instant application. Furthermore, both the methods of Barsky and Allan, et al had demonstrated success. In view of the successful applications of the respective methods, it would have been obvious to one of ordinary skill in the art at the time the invention was made that an anti-ErbB2 antibody coupled to an identifying agent that specifically targets cancerous epithelial cells that over-express ErbB-2 within the breast duct could be delivered by the method of '779 to identify the location of malignant breast cancer within a breast duct or breast ductal network. Because the identifying agent of Allan, et al is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells that over-express the marker to which the targeting molecule binds and because the method of Barsky enables one to deliver the agent directly to the

targeted site at which the cells are expected to occur in a patient, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the combined methodology could be used with a very reasonable expectation of success to identify the location of pre-malignant or malignant cancer in the patient's body.

Finally, it is unclear that Applicants intended to refute that one of ordinary skill in the art would not have known that ductal breast cancer is of breast epithelial cell origin. Nevertheless, without acquiescing to Applicants' argument that the Internet contents of the oncologychannel.com cannot be relied upon to show that ductal breast cancer is of breast epithelial cell origin, it is noted that Lasfargues, et al (1978) teaches that ductal breast cancer is of breast epithelial cell origin. Therefore, in order to simplify the issues, the present rejection cites Lasfargue, et al, but many additional publications published before the invention was made, which teach that ductal breast cancer is of epithelial cell origin, are readily found by searching the PUBMED database.

19. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hou, et al (*Radiology* **195**: 568-569, 1995) in view of McQuarrie, et al (*European Journal of Nuclear Medicine* **24**: 381-389, 1997) and Krag, et al (*New England Journal of Medicine* 339: 941-946, 1998).

Hou, et al teach that which was set forth in the rejection under 35 USC § 102 above. In addition, Hou, et al teach that the contrast material is aspirated or expelled from the breast duct after mammography. However, Hou, et al do not expressly disclose that a compound comprising a targeting molecule coupled to an identifying agent can be used in place of the contrast material when practicing the diagnostic method, wherein the targeting molecule is an antibody or a fragment of an antibody. Furthermore, Hou, et al does not expressly disclose that any unbound coupled compound be eliminated or allowed to exit the breast duct or lymph nodes.

McQuarrie, et al teach a radioimmunoscintigraphic method for identifying the location of malignant breast cancer in patients comprising administering a radiolabeled antibody to the patient and acquiring images using a gamma camera. Specifically, McQuarrie, et al teach that patients received 1, 2, or 4 mg of ^{99m}Tc-labeled monoclonal

antibody that specifically binds a marker expressed by breast adenocarcinoma of epithelial origin (page 382, columns 1-2). Thus, patients were injected with a compound comprising a targeting molecule (i.e., an antibody) coupled to an identifying agent (i.e., a radioisotope). Serial blood samples were drawn before and after the injection of the antibody at successive intervals in order to determine serum clearance of the antibody in the body of the patient (page 382, column 2). Also, urine samples were collected at intervals following the injection in order to determine urinary clearance of the antibody in the body of the patient (page 382, column 2). McQuarrie, et al disclose that urinary excretion was predominant in patients (page 384, column 1). McQuarrie, et al also teach that "on a per patient basis radioimmunoscintigraphy (RIS) showed both a sensitivity and a positive predictive value of 96%" and that "eighty-six lesions were scored as true-positive in the total patient population" (page 385, column 2). McQuarrie, et al conclude, "the ability of this monoclonal antibody to detect tumour both in the primary site and in regional lymph nodes is a significant clinical advantage" (page 387, column 1). The method of McQuarrie, et al does not require the practitioner to remove the unbound radiolabeled antibody from the patient because the antibody is absorbed or naturally clears in the body.

Although McQuarrie, et al do not explicity teach that the regional nodes in which the cancer cells can be detected are the sentinel nodes, Krag, et al teach the first stop along the route of lymphatic drainage from a primary tumor is a limited set of regional lymph nodes and that the lymph nodes that first receive drainage from a tumor are termed sentinel nodes.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the radiolabeled antibody of McQuarrie, et al for the contrast agent of Hou, et al in the method of Hou, et al in order to identify the location of malignant breast cancer in the body of a patient, because Hou, et al teach a method of delivering the antibody directly to the anatomical site where the clinician expects to find cancerous cells and thus, requires less antibody be administered to the patient since not as much of the antibody will be absorbed by non-targeted tissues (e.g., the kidneys) and because McQuarrie, et al teach that the antibody can be used

successfully to localize malignant breast cancer in a patient and furthermore, does not require the practitioner to remove unbound antibody from the patient since the unbound antibody is absorbed and cleared in the body of the patient. One would have been motivated to substitute the radiolabeled antibody of McQuarrie, et al for the contrast agent of Hou, et al in the method of Hou, et al because the specificity of the antibody will enable superior accuracy in localizing the malignancy for the purpose of excising the diseased tissue and because the antibody does not have to be removed by the practitioner from the body of the patient, thus simplifying the procedure.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 31, and 32 of co-pending Application No. 09/565,642 in view of Slavin-Chiorini, et al (*Cancer Biotherapy & Radiopharmaceuticals* **12**: 305-316, 1997), Allan, et *al (British Journal of*

Cancer **67**: 706-712, 1993), and Krag, et al (*New England Journal of Medicine* 339: 941-946, 1998).

In co-pending Application No. 09/546,642, the claims are drawn to a method of identifying the location of pre-malignant or malignant breast cancer within mammalian body comprising a breast duct or breast ductal network, said method comprising a step of providing a coupled compound comprising a targeting molecule coupled to an identifying agent, a step of delivering the agent through at least one breast duct in to identify pre-malignant or malignant cells, a step of identifying the pre-malignant or malignant cells bound by the coupled compound, and a step of identifying the location of the pre-malignant or malignant cells bound by the coupled compound, wherein said step of delivering the agent comprises cannulation or catheterization, or wherein said agent is delivered to more than one duct on a breast, or wherein the cells are identified for the purpose of excising tissue surrounding and including the cells.

The claims in co-pending Application No. 09/546,642 recite the limitation that the unbound coupled compound be allowed to be absorbed and cleared in the body without requiring removal of the unbound compound by the practitioner, while the claims of the present application merely recite that the unbound compound be allowed to be eliminated and/or exit the breast duct. Furthermore, the claims in co-pending Application No. 09/546,642 recite the limitation that pre-malignant or malignant breast cancer cells in a mammalian body comprising a breast duct or breast ductal network be identified, while the claims in the present application recite a limitation that pre-malignant or malignant cells within the breast duct or breast ductal network be identified, or that lymph node involvement be determined by identifying breast cancer cells in the lymph nodes, or more particularly the sentinel nodes.

Slavin-Chiorini, et al teach that a radiolabeled humanized domain-deleted antibody can be used in a radioimmunoscintigraphic diagnostic protocol to localize malignant cancer cells in the body of a patient and which can be allowed to be absorbed and cleared in the body of the patient, and the method, therefore, does not require that the practitioner remove the unbound antibody (abstract).

Allan, et al teach that which has been set forth in the preceding Office actions and reiterated herein. In particular, however, it is noted that Allan, et al teach a method by which both malignant breast cancer cells can be identified in a breast duct or breast ductal network, or in regional lymph nodes.

Although Allan, et al does not teach that breast cancer cells can be identified in the sentinel nodes, *per se*, Krag, et al teach the first stop along the route of lymphatic drainage from a primary tumor is a limited set of regional lymph nodes and that the lymph nodes that first receive drainage from a tumor are termed sentinel nodes.

Given the claims of co-pending Application No. 09/565,642 and the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the coupled compound of Slavin-Chiorini, et al or Allan, et al in method claimed in co-pending Application No. 09/565,642 and to allow any unbound compound to be eliminated and/or exit the breast duct to be absorbed and cleared in the body after diffusing from the breast ductal network, because both Slavin-Chiorini, et al and Allan, et al teach that a radiolabeled antibody, which is absorbed and cleared in the body of the patient so as to not require removal by the practitioner, can be used in a radioimmunoscintigraphic diagnostic protocol to localizing malignant cancer breast cancer cells in a patient's breast ducts, breast ductal network, or lymph nodes, including the sentinel nodes. One would have been motivated to allow the unbound compound to be absorbed and cleared in the body because therefore the practitioner would not be required to remove the unbound coupled compound and accordingly, the catheter would not have to remain in the breast duct during the procedure, or otherwise the patient would not have to be catheterized a second time so that the compound can be removed.

This is a provisional obviousness-type double patenting rejection.

Conclusions

22. No claims are allowed.

23. The art made of record and not relied upon is considered pertinent to Applicants' disclosure. Wahl (1998 and 2001) reviews the state of the art. Kindermann, et al teaches a method for detecting ductal breast cancer.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

S Rawlings
STEPHEN RAWLINGS

slr
May 5, 2003